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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 10/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/743,813	RAMESH ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 72-87 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 72-87 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 24 December 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/12/06 has been entered.

Claims 88-95, drawn to elected invention 2 were canceled as requested. Claims 72-87, drawn to non-elected invention 1, remain pending. The Examiner permits a shift of invention to invention 1 of the restriction requirement set forth on 8/8/05 and shown in the Office Action of 9/7/05.

Claims 72-87, drawn to methods of treating bladder cancer using compositions comprising an oncolytic virus and a transduction enhancing agent that is a mono-, di-, or poly-saccharide with a lipophilic substituent, classified in class 514, subclass 74, remain pending and are under consideration.

Rejections from the previous Action which are not reiterated are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 87 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 87 is incomplete because it does not end in a period.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 72-87 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 72-87 have been amended to require an oncolytic virus that comprises a urothelium-specific promoter. The specification discloses a single example of such a promoter, i.e. the uroplakin II promoter used in recombinant adenovirus CG8840 (see page 15, lines 11-18). The specification does not disclose any other promoter with specificity to the bladder epithelium, nor any virus that specifically infects only bladder epithelium. The specification does not disclose relevant identifying characteristics, such as a correlation between structure and function, that are common to the genus of urothelium-specific promoters. Given this disclosure, one of skill in the art could not

conclude that Applicant was in possession of the claimed genus at the time the invention was filed.

Response to Arguments

Applicant's arguments filed 9/12/06 have been fully considered to the extent that they apply to the rejections set forth above but they are not persuasive. Applicant addresses the rejection at page 12 of the response, arguing that because urothelium specific promoters were well known in the art at the time of the invention as evidenced by US Patent Publication 20020120117, there is no need for them to be further described in the specification. This is unpersuasive. Even if urothelium-specific promoters were known in the art prior to the invention, that would not be evidence that Applicant envisioned their use in the invention at the time the application was filed. There is no evidence of record that Applicant envisioned the use of any urothelium-specific promoter other than the uroplakin II promoter, or any virus comprising a uroplakin II promoter, other than recombinant adenovirus CG8840. For these reasons the rejection is considered proper.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 72, 74, and 83-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (Cancer Res. 62: 3743-3750, 2002), in view of Connor et al (Gene Therapy 8: 41-48, 2001).

Zhang taught that adenovirus CG8840 was a urothelium-specific adenovirus variant that eliminates bladder tumors when administered at 3.33×10^9 pfu in combination with docetaxel. See abstract.

Zhang did not teach administration to the lumenal surface of the bladder, or the use of a transduction enhancing mono-, di-, or poly-saccharide having a lipophilic substituent.

Connor taught that adenoviral infection of urothelium could be improved by treatment of the urothelium with octyl-beta-D-glucopyranoside. Compositions comprising octyl-beta-D-glucopyranoside and 3.5×10^{10} replication deficient adenovirus particles comprising reporter genes were instilled intravesically to rat bladders that were previously washed with PBS, and reporter gene expression was assayed. See abstract and Table 1 on page 42.

It would have been obvious to of one of ordinary skill in the art at the time of the invention to modify the method Zhang by applying the adenovirus to the lumenal surface of a bladder, as taught by Connor, in order to treat bladder cancer. One would have been motivated to use the virus in vivo because this was the whole point of producing the virus (see last sentence of Zhang abstract). One would have been motivated to use lumenal delivery because this allows direct access to superficial tumors, and because Zhang points out that urethral access to bladder tumors (which

leads to lumenal administration) makes bladder tumors appealing targets for viral therapy. It would have been similarly obvious to modify the method of Zhang by treating mouse bladders with octyl-beta-D-glucopyranoside. One would have been motivated to do so to improve access to tumors in the bladder epithelium.

It is noted that Connor did not teach sequential addition of octyl-beta-D-glucopyranoside followed by the adenovirus. However, MPEP 2144.04 (IV)(C) indicates that selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results.

Instant claim 85 requires an oncolytic virus composition of at least 4 X 10^{10} viral particles". The cited art taught administration of adenoviral vectors in the amounts of 10^{9} and 3.5 X 10^{10}. MPEP 2144.05 IIA indicates that differences in concentration will not generally support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In this case the titer of the adenovirus is considered to be a result effective variable that is routinely optimized by those of skill in the art.

Claims 72, 74, and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watanabe et al (Int. J. Cancer 92: 712-717, 2001), in view of Connor et al (Gene Therapy 8: 41-48, 2001) and Mullen et al (Oncologist 7:106-119, 2002).

Watanabe taught treatment of bladder cancer with replication deficient adenovirus carrying a suicide gene in an orthotopic mouse model of bladder cancer. The adenovirus carried a dominant negative version of *ras*, was instilled intravesically, and inhibited the growth of superficial tumors. 10^9 plaque forming units of adenovirus were delivered. See abstract; page 714, column 1, paragraphs 2 and 3; page 715, column 1, first two full paragraphs; and Fig. 4 on page 715.

Watanabe did not teach an oncolytic virus, or the use of a transduction enhancing mono-, di-, or poly-saccharide having a lipophilic substituent.

Connor taught that adenoviral infection of urothelium could be improved by treatment of the urothelium with octyl-beta-D-glucopyranoside. Compositions comprising octyl-beta-D-glucopyranoside and 3.5 $X10^{10}$ replication deficient adenovirus particles comprising reporter genes were instilled intravesically to rat bladders that were previously washed with PBS, and reporter gene expression was assayed. See abstract and Table 1 on page 42.

Mullen taught that oncolytic viruses expressing therapeutic transgenes offered a distinct advantage over analogous replication deficient gene therapy vectors because the virus amplifies itself through several rounds of replication allowing a concomitant increase in transgene expression leading to an amplified antitumor effect. See page 108, column 1, first full paragraph.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Watanabe by treating the mouse bladders with octyl-beta-D-glucopyranoside and to substitute replication competent adenoviruses for

replication deficient ones. One would have been motivated to use octyl-beta-D-glucopyranoside to improve access to superficial tumors in the bladder epithelium. One would have been motivated to substitute an oncolytic virus for the replication deficient virus in order to take advantage of an amplified antitumor effect due to viral replication.

It is noted that Connor did not teach sequential addition of octyl-beta-D-glucopyranoside followed by the adenovirus, but instead added them simultaneously. However, MPEP 2144.04 (IV)(C) indicates that selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results.

Instant claim 85 requires an oncolytic virus composition of at least 4 X 10^{10} viral particles". The cited art taught administration of adenoviral vectors in the amounts of 10^{9} and 3.5 X 10^{10}. MPEP 2144.05 IIA indicates that differences in concentration will not generally support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In this case the titer of the adenovirus is considered to be a result effective variable that is routinely optimized by those of skill in the art.

Claims 72-81 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watanabe et al (Int. J. Cancer 92: 712-717, 2001), in view of Connor et al (Gene Therapy 8: 41-48, 2001), Mullen et al (Oncologist 7:106-119, 2002), and Boer et al (Biochem. Biophys Res. Comm. 166(1): 91-98, 1983).

This rejection is directed to embodiments of the claimed invention that require disaccharides comprising a lipophilic substituent.

The teachings of Watanabe, Connor, and Mullen are summarized above and can be combined to render obvious a method of treating superficial bladder cancer by treating the lumenal surface of the bladder with octyl-beta-D-glucopyranoside and exposing the treated surface to an oncolytic adenovirus. In addition, it is apparent from the teachings of Connor that it was well known in the art prior to the invention that the urothelial glycosaminoglycan layer was an impediment to lumenal administration of adenovirus vectors, and that it was routine in the art to use disruptive agents, particularly detergents, to improve transduction efficiency. In particular, it was routine to optimize the type of detergent that one used to effect transduction, over very broad range of detergents. See paragraph bridging columns 1 and 2 of page 41, and Table 1 on page 42 which discloses 15 different types of detergents, including cationic, anionic, zwitterionic, and 7 different nonionic detergents, that were assayed for their effect on adenoviral transduction of the lumenal surface of the bladder.

These references did not teach a disaccharide comprising a lipophilic substituent.

Boer taught that dodecyl-beta-D-maltopyranoside was a detergent with performance characteristics similar to octyl-beta-D-glucopyranoside. Each was used as a detergent to solubilize vasopressin receptors from membrane preparations.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use dodecyl-beta-D-maltoside as a detergent to improve adenoviral transduction of the bladder urothelium in the invention of Watanabe as modified by

Connor and Mullen. This is because dodecyl-beta-D-maltoside was an art recognized detergent with performance characteristics similar to the octyl-beta-D-glucopyranoside used by Connor in optimizing adenoviral transduction of the lumenal surface of the bladder. It is clear from the teachings of Connor that the identity of the detergent used to improve adenoviral transduction was a result-effective variable that was obvious to optimize at the time of the invention. Thus it would have been obvious to use any art-recognized detergent, particularly those with performance characteristics similar to octyl-beta-D-glucopyranoside.

It is noted that dodecyl-beta-D-maltoside does not have the same stereochemical configuration as the compounds recited in instant claims 75-81 because the hydroxyl group on the #1 carbon of the second (or right-hand) monosaccharide of dodecyl-beta-D-maltoside is in the alpha configuration, whereas claims 75-81 require a beta configuration at this position. However, these stereoisomers are considered to be obvious variants of each other due to their close structural similarity. See MPEP 2144.08(II)((A)(4)(c) which states that if "a species or subgenus is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties", and "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with

improved properties. The utility of such properties will normally provide some motivation to make the claimed species or subgenus." In this case the compounds are so similar that one of ordinary skill would have a reasonable expectation that they would have similar structural properties, and so would be motivated to make the claimed stereoisomer.

Instant claims 79-81 limit the time for which the surface of the bladder is contacted with the detergent or oncolytic virus. These times are considered to be result effective variables that are routinely optimized by those of ordinary skill in the art.

Instant claim 85 requires an oncolytic virus composition of at least 4 X 10^{10} viral particles". The cited art taught administration of adenoviral vectors at a titre of 3.5 X 10^{10}. MPEP 2144.05 IIA indicates that differences in concentration will not generally support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In this case the titer of the adenovirus is considered to be a result effective variable that is routinely optimized by those of skill in the art.

Claims 72-74, 82, and 85 and rejected under 35 U.S.C. 103(a) as being unpatentable over Watanabe et al (Int. J. Cancer 92: 712-717, 2001), in view of Connor et al (Gene Therapy 8: 41-48, 2001), Mullen et al (Oncologist 7:106-119, 2002), and Sedzik et al (NeuroReport 11(11): 2559-2563, 2000).

This rejection is directed to embodiments of the claimed invention that require disaccharides comprising a lipophilic substituent, including those with a cyclohexyl moiety.

The teachings of Watanabe, Connor, and Mullen are summarized above and can be combined to render obvious a method of treating superficial bladder cancer by treating the lumenal surface of the bladder with octyl-beta-D-glucopyranoside and exposing the treated surface to an oncolytic adenovirus. In addition, it is apparent from the teachings of Connor that it was well known in the art prior to the invention that the urothelial glycosaminoglycan layer was an impediment to lumenal administration of adenovirus vectors, and that it was routine in the art to use disruptive agents, particularly detergents, to improve transduction efficiency. In particular, it was routine to optimize the type of detergent that one used to affect transduction. See paragraph bridging columns 1 and 2 of page 41, and Table 1 on page 42 which discloses 15 different types of detergents, including 7 different nonionic ones, that were assayed for their effect on adenoviral transduction of the lumenal surface of the bladder.

These references do not teach a disaccharide comprising a lipophilic substituent, particularly those with a cyclohexyl moiety. These references also do not teach structures set forth in instant claim 72 in which 'X' is a sulfur atom.

Sedzik taught that dodecyl-beta-D-maltopyranoside, decyl-beta-D-maltopyranoside, cyclohexyl-pentyl-beta-D-maltoside, cyclohexyl-hexyl-beta-D-maltoside, octyl-beta-D-thioglucopyranoside, and heptyl-beta-D-thioglucopyranoside were detergents with performance characteristics similar to octyl-beta-D-

glucopyranoside. Each was used as a detergent to solubilize PNS myelin membrane proteins. See abstract, and Table I on page 2560. Note that "Octyl-beta-D-glucoside" is a synonym for octyl-beta-D-glucopyranoside. Note also that the first instance of "cyclohexyl-pentyl-beta-D-maltoside" in "Group B" is a typographical error, and should be cyclohexyl-hexyl-beta-D-maltoside. The molecular weight given for this compound is 508.5, which is the molecular weight of cyclohexyl-hexyl-beta-D-maltoside, not "cyclohexyl-pentyl-beta-D-maltoside". The second instance of "cyclohexyl-pentyl-beta-D-maltoside" in "Group B" gives the correct molecular weight of 494.5. In any event MPEP 2144.09 stated that compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups, are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. As such cyclohexyl-pentyl-beta-D-maltoside is considered to be an obvious variant of cyclohexyl-pentyl-beta-D-maltoside.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use dodecyl-beta-D-maltopyranoside, decyl-beta-D-maltopyranoside, cyclohexyl-pentyl-beta-D-maltoside, or cyclohexyl-hexyl-beta-D-maltoside as a detergent to improve adenoviral transduction of the bladder urothelium in the invention of Watanabe as modified by Connor and Mullen. This is because these compounds were art-recognized detergents with performance characteristics similar to the octyl-beta-D-glucopyranoside used by Connor in optimizing adenoviral transduction of the lumenal surface of the bladder. It is clear from the teachings of Connor that the identity of the detergent used to improve adenoviral transduction was a result-effective variable

that was obvious to optimize at the time of the invention. Thus it would have been obvious to use any recognized detergent, particularly those with performance characteristics similar to octyl-beta-D-glucopyranoside.

It is noted that the maltosides of Sedzik do not have the same stereochemical configuration as the compounds recited in instant claim 82 because the hydroxyl group on the #1 carbon of the second (or right-hand) monosaccharide the maltosides is in the alpha configuration, whereas claims 82 requires a beta configuration at this position. However, these stereoisomers are considered to be obvious variants of each other due to their close structural similarity. See MPEP 2144.08(II)((A)(4)(c) which states that if "a species or subgenus is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties", and "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties. The utility of such properties will normally provide some motivation to make the claimed species or subgenus." In this case the compounds are so similar that one of ordinary skill would have a reasonable expectation that they would have similar structural properties, and so would be motivated to make the claimed stereoisomer.

Instant claim 85 requires an oncolytic virus composition of at least 4 X 10^{10} viral particles". The cited art taught administration of adenoviral vectors in the amounts of 10^9 and 3.5 X 10^{10}. MPEP 2144.05 IIA indicates that differences in concentration will not generally support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In this case the titer of the adenovirus is considered to be a result effective variable that is routinely optimized by those of skill in the art.

Claims 72-81, 86 and 87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watanabe et al (Int. J. Cancer 92: 712-717, 2001), in view of Connor et al (Gene Therapy 8: 41-48, 2001), Mullen et al (Oncologist 7:106-119, 2002), and Amiel et al (WO 02/40630, published 5/23/02).

This rejection is directed to embodiments of the claimed invention that require disaccharides comprising an alkanoic acid residue or a sucrose isomer, as in instant claims 86 and 87, as well as to disaccharides such as lauryl maltoside which is embraced by instant claims 72-81.

The teachings of Watanabe, Connor, and Mullen are summarized above and can be combined to render obvious a method of treating superficial bladder cancer by treating the lumenal surface of the bladder with octyl-beta-D-glucopyranoside and exposing the treated surface to an oncolytic adenovirus. In addition, it is apparent from

the teachings of Connor that it was well known in the art prior to the invention that the urothelial glycosaminoglycan layer was an impediment to lumenal administration of adenovirus vectors, and that it was routine in the art to use disruptive agents, particularly detergents, to improve transduction efficiency. In particular, it was routine to optimize the type of detergent that one used to affect transduction, over very broad range of detergents. See paragraph bridging columns 1 and 2 of page 41, and Table 1 on page 42 which discloses 15 different types of detergents, including cationic, anionic, zwitterionic, and 7 different nonionic detergents, that were assayed for their effect on adenoviral transduction of the lumenal surface of the bladder.

These references do not teach disaccharides comprising a lipophilic group, particularly an alkanoic acid residue.

Amiel taught a variety of detergents that could be used as alternatives to octyl-beta-D-glucopyranoside, including sucrose monolaurate and dodecyl maltoside. Note that, similar to Connor, Amiel taught that TWEEN-20 and TWEEN-80 were also alternatives to octyl-beta-D-glucopyranoside. See page 11, lines 6-12 of Amiel, and Connor at page 42, Table 1.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use sucrose monolaurate or lauryl maltoside (i.e. dodecyl-beta-D-maltoside) as a detergent to improve adenoviral transduction of the bladder urothelium in the invention of Watanabe as modified by Connor and Mullen. This is because these compounds were art recognized detergents with performance characteristics similar to the octyl-beta-D-glucopyranoside used by Connor in optimizing adenoviral transduction

of the lumenal surface of the bladder. It is clear from the teachings of Connor that the identity of the detergent used to improve adenoviral transduction was a result-effective variable that was obvious to optimize at the time of the invention. Thus it would have been obvious to use any art-recognized detergent, particularly those with performance characteristics similar to octyl-beta-D-glucopyranoside.

It is noted that the detergents of Amiel may not have the same stereochemical configuration as the compounds recited in instant claims 75-78 or 86 and 87. However, stereoisomers are considered to be obvious variants of each other due to their close structural similarity. See MPEP 2144.08(II)((A)(4)(c) which states that if "a species or subgenus is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties", and "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties. The utility of such properties will normally provide some motivation to make the claimed species or subgenus." In this case the compounds are so similar that one of ordinary skill would have a reasonable expectation that they would have similar structural properties, and so would be motivated to make the claimed stereoisomer. See also MPEP 2144.09 which

indicates that stereoisomers of similar functions are obvious over each other. In this case, the various stereoisomers would all be expected to function as detergents.

Response to Arguments

Applicant's arguments filed 9/12/06 have been fully considered to the extent that they apply to the rejections set forth above but they are not persuasive. Applicant addresses the rejection at pages 11-14 of the response.

Applicant argues that not all detergents would be effective as transduction enhancing agents because the function of the transduction enhancing agents of the instant invention is not cell membrane solubilization, but glycosaminoglycan layer permeabilization. This is unpersuasive. Applicant has not shown that the structural characteristics required for membrane solubilization are any different than those required for GAG permeabilization, or that compounds that cause membrane solubilization would not be expected to be useful for increasing tranfection of bladder epithelium. One of ordinary skill in the art understands how detergents function, and understands what are the structural characteristics that contribute to detergent function. It was clear to those of ordinary skill in the art at the time of the invention that detergents having a wide variety of structures had been used to improve adenoviral transduction of bladder epithelium, and that it was routine in the art to investigate the abilities of various detergents to improve adenoviral transduction of bladder epithelium. See Connor and Amiel, above. In view of the fact that disaccharide detergents were known to have similar detergent characteristics to octyl-beta-D-glucopyranoside, it clearly would have

been obvious to use these detergents to enhance delivery of adenoviruses to bladder epithelium.

Applicant relies on Ramesh (Mol Ther. 10(4):697-705, 2004) to provide evidence that one of ordinary skill in the art would not expect compounds of similar structure to function similarly in the clamed method. However, Ramesh provides evidence of just the opposite. Out of eight alkyl disaccharides tested, seven provided varying levels of transfection, and only one provided no detectable transfection. This is objective evidence that one could readonably expect structurally similar compounds to provide similar results in the claimed method.

At page 14 of the response Applicant argues that the instant specification provides data at pages 37 and 41 showing that the effectiveness of a monosaccharide transducing agent is not predictive of the effectiveness of the corresponding disaccharide, so one of skill in the art would not have had a reasonable expectation of success in combining the cited references. Applicant also argues that that although Sedzik taught that various lipophilic disaccharides are equivalents to octyl-beta-D-glucopyranoside for use as a detergents, it would not be obvious to substitute any of these lipophilic disaccharide detergents for octyl-beta-D-glucopyranoside to improve efficiency of oncolytic adenovirus infection of bladder epithelium. This is based on the fact that the specification discloses at page 41, lines 4-5 that n-dodecyl-beta-D-glucopyranoside showed "little or no enhancement of bladder transduction", and on the opinion that the performance characteristics of detergents in solubilizing membrane

proteins are not suggestive of their relative abilities to enhance transduction in the bladder epithelium.

Applicant's arguments are unpersuasive. Even if one of ordinary skill in the art at the time of the invention was aware of the teachings of the instant specification, the result of "little or no enhancement of bladder transduction" would not lead one away from using other detergents in the process of optimizing adenoviral transduction of bladder epithelial cells, particularly in light of the fact that Connor showed in the prior art that a variety of detergents including octyl-beta-D-glucopyranoside improved adenoviral infection of urothelium. It was clear from the teachings of both Connor and Amiel that it was routine in the art to use detergents to improve adenoviral transduction of the bladder epithelium, and that in the process of optimization a wide variety of structures were used. So it is clear from these teachings that the identity of the detergent used to improve adenoviral transduction was a result-effective variable that was obvious to optimize at the time of the invention. Thus it would have been obvious to use any art-recognized detergent, particularly those with performance characteristics similar to octyl-beta-D-glucopyranoside, which Connor showed improved adenoviral transduction of bladder epithelium. To the extent that Applicant's argument is based on unexpected results (e.g. that Applicant surprisingly found that structurally similar compounds had unexpectedly different effects when used in the claimed method) the argument is unpersuasive. MPEP 716.02(b) indicates that evidence relied upon to establish that results are unexpected and non-obvious should of both statistical and practical

significance. There is no statistical analysis of the data presented at pages 37 and 41, so it cannot be considered to be statistically significant.

For these reasons the rejections are considered proper.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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